REVIEW ARTICLE

Personalized Gut Microbiota-Driven Therapies in Precision Microbiome Medicine

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Abstract

The microbiome plays a key role in the maintenance of our health, the causes of our ailments, and our recovery from treatment. With the recent advances in the integration of multiple omics techniques, systems bioinformatics, and predictive modeling, a new frontier in microbiome research that leverages personalized microbial profiling with purpose-driven clinical goals is on the rise. The purpose of this review is to describe the overall concept of Precision Microbiome Medicine (PMM), including the clinical promise, underlying principles, and the enabling technologies. It begins with a discussion of the temporal dynamics and the bidirectional cross-talk between the gut microbiome and the body systems. It also discusses the technologies that are critical for the development of PMM, including, but not limited to, high-throughput sequencing, metagenomics, metabolomics, and machine learning, along with real-time surveillance systems. The review analyses the application of PMM in a number of disease areas, including inflammatory bowel disease, metabolic syndrome, and cancer, with a strong focus on microbiome diagnostics, prognostics, and personalized therapy. Other therapeutic approaches discussed include engineered microbial consortia, microbiota-directed diets, prebiotics, probiotics, and personalized therapy. The review also addresses the barriers to broader implementation of PMM, including issues of causal inference, lack of standardization, and ethical constraints. Finally, this review strongly discusses the future goals, like microbiome-based digital therapies collaborating with precision nutrition, which can monitor the microbiome for longer periods with clinical translation guidelines. This conceives new ideas with significant future possibilities to explain the significance of PMM in customized health care.

Key words: Diseases, personalized therapy, prebiotics, precision medicine, precision microbiome medicine

INTRODUCTION

Precision medicine (PM) symbolizes a type of medicine that implies the integration of a set of details that contains the patient's heredity, environment, and social behavior to diagnose, treat, or prevent the disease or disease condition. PM: Concept and Tools.[1] Kuntz and Gilbert introduced precision microbiome medicine (PMM) is a type of PM that uses person's microbiome data to prevent, diagnose, and treat the diseases.[2] Because microbiomes

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quality is unique and are influencing individuals' health and disease state by impacting their endocrinology, physiology, and neurology.[3]

There are trillions of microorganisms in the human gut microbiota, including bacteria, viruses, fungi, and archaea. It is a complex and diverse ecosystem. It is very important for keeping the health in good condition because it affects digestion, the immune system, and metabolic homeostasis. Researchers and medical professionals all over the world are interested in this unusual group of microbes because they have a huge effect on human health and disease, making them a key target for personalized medical treatments. Hence, human gut microbiota is emerging as one of the PMs nowadays.[4] Because they are unique to each individual and are playing an essential role in the individual's immunity and health, disease susceptibility, and response to drugs.[5,6]

There is a lot of variation in gut microbiota between people, which makes it difficult to promote PM in cardiovascular diseases (CVDs).[7] Although this variability poses some difficulty the variability also offers a chance to have an individualized treatment of the individual with that unique set of microbes. There is substantial evidence indicating that gut microbiota plays a crucial role in human health and disease across various pathological conditions.[8] Dysbiosis, which is a form of imbalance in the intestinal microbiota, has been linked to most long-term health complications such as obesity, diabetes, inflammatory bowel disease (IBD), and neurological disorders.[9] It has been demonstrated that dysbiosis, the imbalance between the microbial composition of the gut, is associated with a variety of metabolic diseases, which can demonstrate that microbial-focused treatments can be effective.[10] This dysbiosis condition has predisposed the microbiome as a biomarker and a therapeutic target, and this creates new opportunities of PM.[11]

The latest technological developments have seen the gut microbiome actively studied and modified in a manner not previously possible. This is more so with new technologies in next-generation sequencing and metabolomics. These technologies enable us to develop highly fined and accurate details of microbiome communities and their genetic composition and the chemicals they secrete.[3] The technologies associated with high-throughput sequencing have transformed the manner in which -omics databases are created, and it can now study the human gut microbiome in significant detail.[12] Such new technologies have provided an opportunity to develop more sophisticated methods of analysis where disparate types of data are merged together to provide a more informed picture of that which the microbiome does and how it can be adapted to treat diseases. Modern therapy modalities in PMM are much further enhanced than the historic use of probiotics therapy. The field of artificial microbiome therapeutics has expanded from probiotics and fecal transplants to encompass community consortia, engineered probiotics, and specific metabolites. This is because the safety and regulatory issues that used to slow down progress in this area are no longer a problem.[3] Fecal microbiota transplantation (FMT), engineered probiotics, and microbiome-derived metabolites are some new treatments that could help fix immune problems and make treatments work better.[13] These new methods are a big change from treatments that work for everyone to treatments that are very specific to each person.

The action of gut microbiota on drug metabolism and effectiveness is a significant area on research in PM. The gut microbial composition potentially affects the drug metabolism, toxicity, and efficacy, underscoring the need of personalized pharmacotherapy.[14] Past 10-year research on this field shows they are effective. This proves nature of gut microbiota can differ from person to person.[15] This knowledge helps the physicians to make the decision, PMM uses FMTs and probiotics indicating how people with IBDs are treated (pooled effect size = 0.77, 95% CI: 0.710.83).[16] Artificial intelligence (AI)-based diagnostic tools, including Random Forest and QSAR models, exhibited superior diagnostic capabilities (pooled effect size = 0.87, 95% CI: 0.800.94).[16] These findings demonstrate the potential of integrating microbiome science with PM to transform disease treatment methodologies. Personalized medicine is another significant specialized in PMM. It is based on the persons gut microbiota, which could improve the health conditions.[17] It is the type of precision approach based on individual's unique traits. It offered promise in altering the makeup of the gut microbiota directly.[18]

Although more strides have been achieved to date, there is still a multitude of challenges, which must be overcome before microbiome-based PM can be implemented in numbers of clinical settings routinely. These developments into practice are still riddled with challenges like inter-individual variability of microbiomes, lack of full mechanistic insights, and regulatory challenges.[13] However, even though there are positive initial results, the practical use of microbiome-based approaches in real clinical settings is still impeded by the heterogeneity of patients, ethical dilemmas, and regulatory limitation.[19] The impediments hindering clinical implementation should be overcome by investing in research and development continuously. Increment of our understanding of the dynamics of the microbiomes and optimization of therapeutic modalities will be strategic moves toward this goal. In the future, the integration of microbiome science and precision-based medicine promises a breakthrough in the transformative management of healthcare provision. Taking the multi-omics approach and pushing microbial therapeutics to the next level, the gut microbiome can be turned into a supportive technology almost instantly and become a cornerstone of PM.[13]

The multidisciplinary strategy would help to improve patient results in the age of PM, as it can indicate how complex the connections between the microbiome and the human body are.[12]

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This represents a general assessment of the current state and future of the precision of microbiome medicine, or more precisely, the targeted gut microbiota-based therapies. We look into the future of biology that drives microbiome-host communication, evaluate the existing therapies, discuss technological breakthroughs that enable precision treatments, and discuss the opportunities and challenges that the rapidly evolving field will encounter in the future. Our purpose in conducting this analysis is to assist us in future planning on how to use PMM within the clinic and to expand it. We want to go to improved, more bespoke healthcare options that take advantage of the strength of our microbial allies.

COMPONENTS OF PMM

The integration of the microbiome into medicine promises to utilize the interdependent and multiplex relationship between the microbiome and human physiology to achieve personal mental and physical health management and treatment.[20,21] Three key elements in its development can be attributed to advanced technologies of microbiome profiling, metabolomic and host-integrated analysis, and predictive modeling through the use of AI [Figure 1].[22,23]

Microbiome profiling technologies

New technology in sequencing and multi-omics has dramatically changed the breadth and depth of microbiome studies, which is the basis of PMM. Methods like 16S ribosomal RNA (16S rRNA) gene sequencing, shotgun metagenomics, metatranscriptomics, metaproteomics, and metabolomics can be used to profile the gut microbiomes,[24] SHIME® (Simulator of the Human Intestinal Microbial Ecosystem), Human Microbial X (cross) talk (Humix), and RapidAim (Rapid Assay of Individual Microbiome).[25]

16S rRNA sequencing uses the hypervariable fragments of the bacterial 16S rRNA gene to identify the bacteria at genus or species level. It is not very expensive and is commonly applied, yet it is not very broad regarding synchronizing highly connected strains and proficiencies.[26] 16S rRNA gene sequencing and shotgun metagenomic methods were used by Elie *et al*. to understand the *Clostiridium difficile* infections (CDI).[27] Dysbiosis-associated cancer patients' gut microbiome was studied with 16SrRNA gene sequencing by Li *et al*. The study collected stool samples from 33 endometrial cancer patients and healthy volunteers between February 2021 and July 2021. The abundancy of Proteobacteria, Gammaproteobacteria, Enterobacteriales, Enterobacteriaceae, and *Shigella* screened from endometrial cancer patients.[28]

By contrast, shotgun metagenomics sequences all microbial DNA in a sample and provides both strain-level resolution and rich functional annotation. This technique will help in proper detection of microbial genes with regard to host-microbiota interactions, antibiotic resistance, and pathogenicity.[29] The overlap of oral and gut microbiota in healthy adults was studied by MULTI-cohort shotgun metagenomics analysis. The research established the observation of ectopic colonization of oral microbiomes at the distal region of the gut of healthy adults.[30] In another study, whole-genome shotgun metagenomics sequencing was used to reveal the decreased microbial groups in obese cats.[31]

To combine both taxonomic and functional information, metatranscriptomics measures the currently active microbial gene expression profile through total RNA sequencing. This gives an insight into the process of metabolism and bacterial action in real-time under physiological conditions or diseases.[29] Martínez-Nava *et al*. used pyruvate and amino acid metabolism-associated genes from gut microbiomes for hyperuricemia and gout conditions in humans. The study used RNA sequences extracted from 26 fecal samples: Six

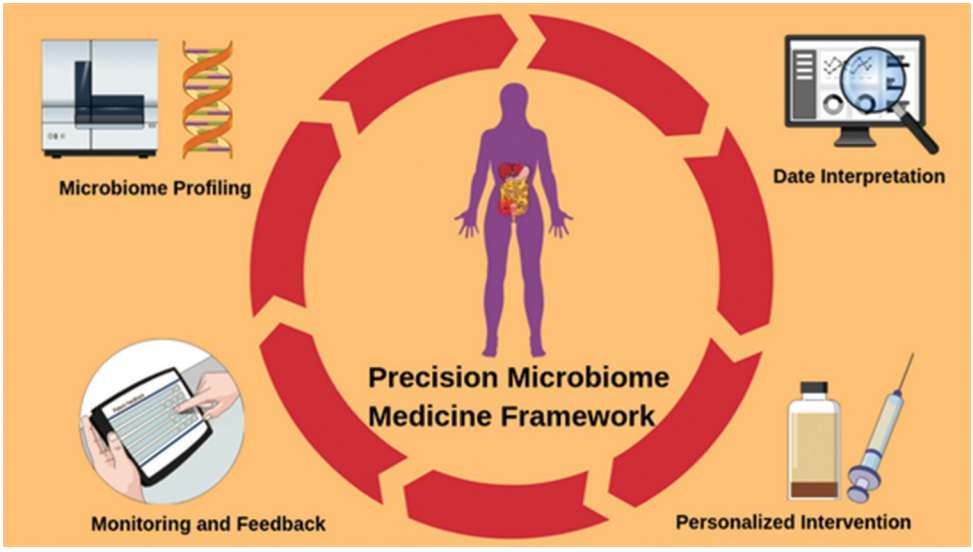

Figure 1: Overview of precision microbiome medicine workflow

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from gout patients, ten from asymptomatic hyperuricemia patients, and ten from normouricemic individuals.[32]

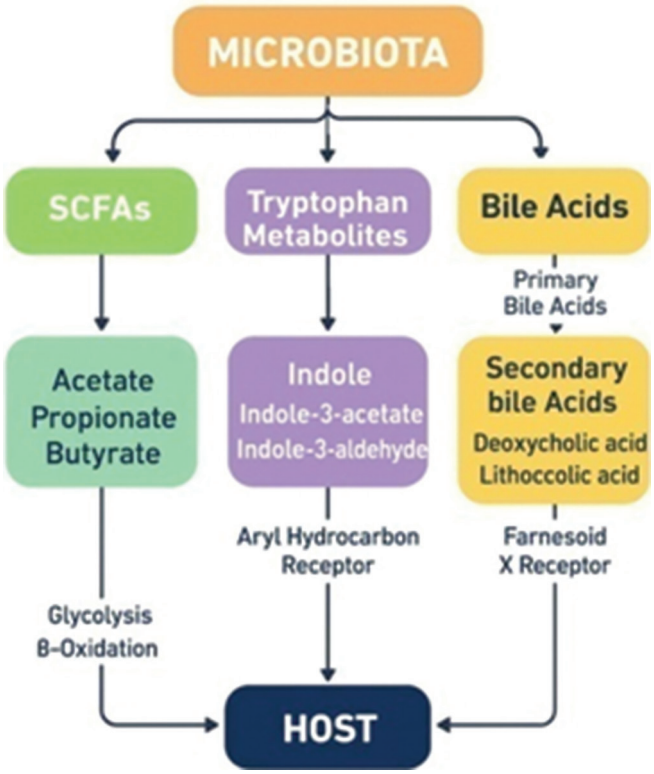

Figure 2: Microbiome-derived metabolites pathway

These processes in combination give an architecture of microbiome in a multi-dimensional picture.

Peel, on the other hand, metabolomics will be another key to focus on the study of bioactive small molecules in the host microbe-interactions possibly representing the functional output of the microbiome [Figure 2 and Table 1]. Metabolites are critical biomarkers and targets of treatment in the case of metabolic syndrome (MetS), IBD, and depression.[33] A serum metabolome study explored the therapeutic mechanisms of the Tongfeng Qingxiao prescription in treating gouty arthritis.[34] Short-chain fatty acids such as acetate and butyrate that adjust host immunity and epithelial health; bile acids that undergo adjustments by intestinal microbes and mediate cholesterol metabolism; and tryptophan-derived metabolites that adjust neurotransmission and inflammation are all quite notable.[35]

In addition, the addition of host genomics and epigenomics to the microbiome data enhances clinical relevance. Microbial composition could be molded by a host genetic variation, and the epigenetic alterations can translate microbiome-driven alterations in gene expression.[36] Cross-referencing host and microbial data will allow the researcher to gain insightful understanding of individual disease vulnerabilities and responsiveness to interventions resulting in personalized treatment.

Table 1: Key microbial metabolites and their host effects

Metabolite	Microbial source	Physiological role in host	Associated health effects	References
Acetate	Bacteroidetes, Firmicutes	Energy source for colonocytes; regulates appetite through central mechanisms	Reduced in inflammatory bowel disease (IBD)	[37]
Propionate	Bacteroidetes	Inhibits cholesterol synthesis; modulates gluconeogenesis and immune function	Protective in obesity and type 2 diabetes	[37]
Butyrate	Firmicutes (e.g., *Faecalibacterium*)	Major energy source for colon cells; anti-inflammatory; maintains gut barrier integrity	Low levels linked to colorectal cancer and IBD	[38]
Secondary Bile Acids	*Clostridium*, *Eubacterium* spp.	Modulate Farnesoid X receptor and G protein-coupled bile acid receptors; lipid metabolism and immune activity.	Excess linked to colon cancer; moderate levels is beneficial to the metabolism	[39]
Tryptophan metabolites	*Lactobacillus*, *Bacteroides* spp.	Precursor of serotonin; regulates immune and gut-brain signaling through AhR receptor	Dysregulation implicated in depression and IBS	[40]
Trimethylamine	*Desulfovibrio*, *Clostridia* spp.	Reduced to Trimethylamine-N-oxide in liver; modulates the process of cholesterol and atherosclerosis pathways	Higher levels associated with cardiovascular disease	[41]
Lipopolysaccharides	*Escherichia coli*	Activates innate immunity through Toll-Like Receptor 4; causes inflammation	Elevated levels induce metabolic endotoxemia and insulin resistance	[42]

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AI and predictive modeling

AI refers to the ability of the machine to perform the operations that are necessary to the human intelligence, whilst Machine Learning (ML) is a subdivision of AI which is working on the algorithms that would enable the computer to gather data and forecast the data.[43] Microbiome data, as complex, high-dimensional makes the application of AI and ML obligatory to analyze and interpret. These tools are inseparable in the processes of determining the patterns of microbial occurrence related to diseases and the determination of clinical outcomes. Random forest of ML, support vector machine, and neural networks are able to prefigure the microbial signatures indicative of disease.[44] The models allow studying thousands of microbial characteristics to identify patterns that cannot be fully appreciated using standard statistical tools.[45] Risk stratification is another area of AI contribution, as it is possible to categorize patients according to microbiome profiles as being at a high or low risk of diseases. The ML models in therapy prediction have been applied to predict the response to an intervention (e.g. immunotherapy or probiotics), such as type of microbiome to which a patient will be exposed to.[46]

Besides, AI has been used to create individualized diets based on the prediction of the effect of particular foods on microbiome and the metabolic profile of an individual and nuance-based interventions. MICOM integrates genome-scale metabolic models to model inter-microbial and host-microbe interactions as well as to predict metabolic response to different conditions.[47] MIMOSA2 incorporates taxonomic and metabolomic data to identify the microbes behind the metabolite levels to help in functional interpretation.[48] The Gut MicroNet network-based visualization tool lets the user view the relationships between the disease or host phenotype and microbial taxa.[49] Finally, MicrobiomeAnalyst is an easy-to-use interface of all statistical, functional, and visual analysis of microbiome data that enable users to support simple diversity measures and reach discovery levels of biomarkers.[50] Such AI-based tools will help close the gap between the challenging microbiome data and clinically informative data in the microbiome field, making PMM a leading field in the personalized care of patients [Figure 3 and Table 2].

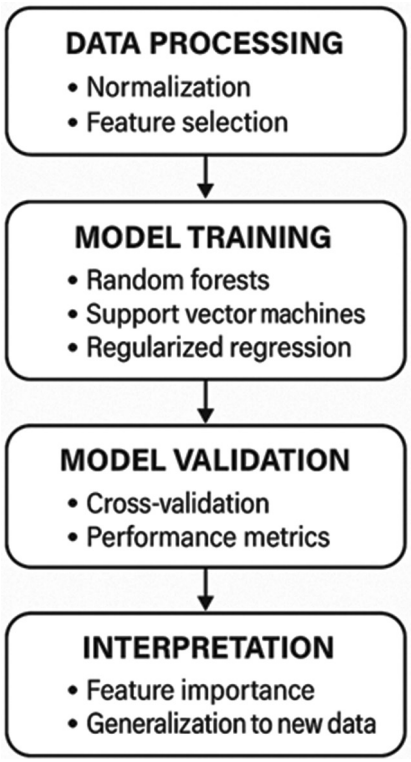

Figure 3: Machine learning pipeline for microbiome analysis

APPLICATIONS IN CLINICAL MEDICINE

PMM: Toward personalized gut microbiota-driven therapies

Every person carries a different microbiome, and this makes him/her unique. The medicines specifically tailored to each patient that is especially important to achieve efficient and accurate therapeutic outcomes are the use of which is vital. This is actually intended to meet the special needs of every individual, taking into account their genetic composition, psychological causes, way of life, clinical traits, and biomarkers.[46,53] To cure the metabolic diseases, the application of omics would be implemented, and validation of the biomarkers in the personalized microbiome-based therapies.[54]

Personalized nutrition

The notion of customized nutrition has surfaced from the diverse metabolic responses individuals exhibit to various food components. While this notion has been examined, recent studies have examined the possible effects of genetic variations on the gut microbiota. In a study, among 121 IBS patients, 71 were assigned to personalized nutrition, and 51 were to FODMAP diet. The personalized diet approach significantly reduced the IBS symptoms, enhanced quality of life, and notably diversity change was observed in gut microbiome.[55] Moreover, the dietary changes can easily affect the gut flora, which is person-specific. Consequently, the impact of customized meals on gut microbiota has been established in a number of recent research.

Microbiome-associated dietary intervention in diseases

The gastrointestinal (GI) system houses most of the body's microorganisms and serves as a site for immune interactions between the intestinal microbiota and the host.[56] The gut microbiota is thought to be connected to a number of immunological and GI disorders.[57] Apart from gut

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Table 2: Features of AI tools for microbiome analysis

Tool	Primary function	Data inputs	Key outputs	Accessibility	References
MICOM	Constraint-based metabolic modeling of microbial communities	Metagenomic data, taxonomic profiles, metabolic models	Community metabolic fluxes, growth predictions	Python-based (open-source)	[47]
MIMOSA2	Integration of metabolomics and microbiome data to infer microbial metabolic activity	Microbial taxa, metabolomic profiles	Contribution scores of taxa to metabolite levels	R package and web interface	[48]
GutMicroNet	Network-based visualization of microbe–disease and gene interactions	Taxonomic profiles, disease metadata, gene info	Interactive networks of microbiome-disease relationships	Web-based platform (open access)	[49]
MicrobiomeAnalyst	Comprehensive statistical and machine learning analysis of microbiome data	OTU/ASV tables, metadata	Alpha/beta diversity, differential abundance, biomarkers	Web-based+R package	[50]
SIAMCAT	Supervised learning and feature selection for microbiome classification	Microbiome feature matrix, sample labels	Feature importance, cross-validation performance metrics	R package (command-line)	[51]
Qemistree	Tree-based visualization and ML on metabolomics data with microbe linkages	LC-MS spectra, metadata	Molecular feature trees, metabolite–microbe relationships	Web and Python (Qiime2 plugin)	[52]

microbiota, dietary factors are essential for promoting GI health and treating associated illnesses. Ghosh *et al*. altered gut microbiomes in older people to control aging disorder. The study was done up to 1 year MedDiet to analyze gut microbiota could reduce frailty. The gut microbial metabolites were changed due to diet, and there is an increased level of short-chain fatty acids and a reduction in secondary bile acids, p-cresols, ethanol, and CO_2.[58] Similarly, isocaloric Mediterranean intervention improved overall metabolic health by enhancing gut microbiomes and their metabolomes in 82 healthy overweight obese category who all are regularly following vegan diet.[59]

To ease symptoms in people with GI diseases, numerous nutritional methods have been established. Probiotics, postbiotics improve health and treat diseases.[60,61] They effectively improved gut-kidney axis by modulating autophagy signaling pathway. Four strains of *Lactobacillus* and two *Bifidobacterium* were treated dextran sulfate sodium-induced colitis in mice model. The combination upregulated the autophagy-related genes.[62] The postbiotic products of *Limosilactobacillus fermentum* injected into cisplatin-induced chronic kidney disease in mice model. Both the strain and its culture supernatants were regularly supplied through water. After 28 days, the combination drastically reduced the blood urea nitrogen, creatinine, reactive oxygen species formation, lipid peroxidation, and improved total antioxidant effects and renal protection effect was confirmed in histopathological study.[63] However, their application in the medical field is forced by public acceptance and regulatory limits, as they are branded as health products rather than drugs.[64]

For people with irritable bowel syndrome (IBS), low-fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diet has been designed. It has been established that the low-FODMAP diet reduces the consumption of indigestible or slowly absorbed carbohydrates, which helps to relieve the symptoms of IBS.[55,65] For instance, research has demonstrated that people with IBS respond differently, influenced by the pre-existing conditions of precise gut microbiota after consuming a low-FODMAP diet.[55,65-67]

Dietary fibers, like resistant oligosaccharides such as inulin, fructo-oligosaccharides, and galacto-oligosaccharides are considered as prebiotics.[68] Prebiotics are the substances that can effectively enhance the gut function, metabolic and metal health, and bone strength. Apart from the dietary fibers, the latest studies identified the response of gut microbiomes with polyphenols, indicating they can be used as prebiotic sources.[69] Polyphenols are the type of secondary metabolites which are distinguished by aromatic rings with one or more hydroxyl groups in their molecular structure, ranging from simple phenolic compounds to multifaceted high-molecular-weight polymers. These compounds have low bioavailability and undergo extensive metabolism in the large intestine, facilitating interactions. In fact, it has a bidirectional relationship in which polyphenols influence the

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composition and the functions of the gut microbiota and as well as in which the microorganisms are able to influence bioactivity of phenolic compounds. These interactions may control the metabolic pathways and bioavailability of polyphenols, converting them into metabolites that could have varied effects on host health.[69] Lignans are metabolized in the phenolic and alcohol pathway, which helps in prevent oxidative damage of low-density lipoprotein compounds and maintaining normal function in the respiratory and GI tracts.[70]

Regular consumption of dietary polyphenols is associated with a low risk of cardiometabolic disorders.[71-73] Web-based 24 h dietary recalls over 1 year showed intake of total polyphenol, flavonoid, and phenolic acids lowering the MetS associated with cardiometabolic risk factors.[71] In polycystic ovarian syndrome, the dietary polyphenol intake controlled oxidative stress.[73] Furthermore, cross-sectional study with 404 Iranian obese and overweight women group confirmed following the total polyphenols diet significantly reduced the body mass index (BMI) and weight-to-hip to hip ratio, and insulin resistance.[72] This ensures polyphenol's anti-diabetic, anti-inflammatory, anti-lipidemic, and anti-oxidant characters. However, the health aspects of dietary polyphenols barely depend on how they are metabolized and absorbed. It also influences the quality and activities of gut microbiomes. Based on the food source, the polyphenols prebiotic effect may get change.[74] While polyphenols are currently acknowledged for their role in modifying gut microbiota composition, definitive evidence of their prebiotic effects remains elusive.

Microbiome-guided pharmacotherapy

Engineered probiotics for controlled delivery of therapeutic molecules

It is established that the GI microbiota is important in the maintenance of general homeostasis.[75] However, changes in such a microbiome can lead to the acquisition and worsening of illnesses. These complex ecosystems have between 100 and 1000 species of bacteria, and each of them may react with the host differently. Therapeutics and microbiome-based biomarkers are the two types of microbiome-based drugs. Probiotics are intended to release dynamic components within the Tumor Micro Environment, including cytokines, nanobodies, α-hemolysin, immunomodulatory proteins, enzymes that convert prodrugs, and toxins.[76] This influences the capacity of engineered probiotics to take over tumors, allowing the direct distribution of therapeutic drug molecules to the tumor site. Young *et al*. utilized recombinant *Mycobacterium smegmatis* to treat tumors; it gives tumor additional adjuvant effects, thus is effective as a cytokine delivery vehicle.[77,78] Mice with breast cancer had their tumor cells injected with recombinant *Bifidobacterium longum* stating cytosine deaminase (eCD). eCD can change the administered 5-fluorocytosine into 5-fluorouracil (5-FU), thereby promoting intratumoral 5-FU concentrations and decreasing tumor size.[79] *Escherichia coli* modified by to release cytokines was found to target adenomas effectively in mouse models when given orally. This oral administration of the strain decreased the adenoma burden by about 50%, and the altered EcN delivered blocking nanobodies at the neoplastic site.[80] The notion of altering the GI microbiota to recover health outcomes has become widely putative in modern medicine.

Over the recent years, the cases of cancer are being recorded in large numbers, and this situation could be attributed to the transformations in lifestyle, rapid urbanization, air pollution, and ageing.[81] The reason that is explained by Forbes *et al*. is the effects of the use of genetically engineered bacteria in the treatment of cancer.[82] These are developments in addition to extending the clinical uses of probiotics but also and further to understand how they work.

FMT 2.0

FMT and gut microbiota

The gut microbiota, commonly referred by the term "invisible organ," is essential to maintaining human health. It consists of more than 100 trillion microorganisms with an overall genome that is vastly surpassing those of human beings and contributes to crucial body processes such as intestinal homeostasis, immunological regulation, and digestion.[83] There is an increasing connection between the gut-brain axis, which is an interconnection between the gut and the central nervous system, and the occurrence of neurological and psychiatric disorders. Patients of the neurological diseases complain of the GI symptoms, and patients note that the gut plays a key role in the development of the disease and the creation of treatment options that manage the microbiota. At present, used methods include FMT, which has been shown to be the most effective intervention, probiotics, prebiotics, synbiotics, and antibiotics.[11] FMT restores microbial balance in the GI tract of a patient by introducing stool from a healthy donor. By altering the gut-brain axis, it is known to reduce neurological and psychological disorders in addition to GI symptoms.[11] FMT was first proposed 1,700 years ago by the Chinese doctor Ge Hong, who treated severe diarrhea and food poisoning with fecal suspensions.[84] In the 1950s, Stanley Falkow developed an experimental method of creating fecal capsules in surgical patients on antibiotics, but this was not adopted, and no publication of the results was ever done (Out, 2016). FMT has been approved by the Food and Drug Administration (FDA) as a treatment for recurrent *Clostridium difficile* infection (rCDI) and has an 80–90% success rate.[85,86] Dysbiosis (microbial imbalance) has been involved in a wide range of diseases, including GI disorders, Type 2 diabetes mellitus,[87] MetS,[8] autoimmune,[88] neuropsychiatric diseases,[89] obesity,[90] IBD, IBS,[91] decompensated cirrhosis,[92] cancers,[93] and graft-versus-host

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cancer.[94] A disturbed gut microbiota has been linked to Parkinson's disease, epilepsy, autism spectrum disorder, multiple sclerosis, and Alzheimer's disease.[95-99] These diseases associated with alterations to the gut microbiota and associated to FMT delivery methods are listed in Table 3. The broad spectrum of FMT techniques used in preclinical and clinical trials, along with the wide range of microbial taxa involved, is described. Its primary therapeutic effects include resolving dysbiosis and restoring microbial diversity. FMT itself is now under investigation in various conditions, such as MetS, multiple sclerosis, hepatic encephalopathy, IBD, and IBS, though it has only been licensed against rCDI.[100-103]

FMT engraftment, donor selection, and administration methods

Donor strain engraftment after FMT varies greatly between patients, influenced by factors such as mixed delivery routes (upper and lower GI), prior antibiotic use, and the presence of infectious diseases. These factors might explain why FMT is more often effective for rCDI than for chronic or non-infectious conditions.[104] Since FMT has typically been performed on ill individuals and not on healthy volunteers, it is not yet determined whether the increased rate of engraftment of proinflammatory microbes is a resultant effect of their own phenotypic properties, such that they tend to propagate and establish further in a new habitat or is simply secondary to their accommodation to an inflamed and dysbiotic environment. Even though refined microbial consortia may not spread harmful microbes (including pathogens that screening may not find),[105] it is still not clear if these consortia can be a good alternative to the complicated process of FMT.[106] The mechanisms and dynamics that establish the attaching ability of the donor microbes to the recipient is not well understood. Very few donor-recipient pairs have been studied in the beginning to see how donor strains spread to the recipient. The availability of larger FMT trials and the progress made in strain-resolved metagenomics made it possible to do more in-depth analyses that began to reveal how well FMT works across diseases. This resulted in the development of statistical models that are capable of estimating the post-FMT microbiome composition.[107] These kinds of studies were only done on one group of people,[108] and there were still questions about whether the results could be applied to other groups or conditions. There is now the possibility of deeper strain level metagenomics,[109-111] and

Table 3: Altered gut microbiota and FMT administration techniques in different diseases

S. No.	Disease	Altered gut microbiota	FMT delivery method	References
1.	Diabetic kidney	Odoribacteraceae	Rectal probe FMT in mice	[90]
2.	Diabetes	*Desulfovibrio*, *Bilophila*, *Lactobacillus*, *Anaerotruncus*, Rikenellaceae	Transendoscopic enteric tube, nasojejunal, autologous and allogenic FMT	[125]
3.	Obesity	*Faecalibacterium*, *Escherichia coli*, *Roseburia*, *Lactobacillus*	Oral capsule and endoscopic FMT	[90]
4.	Metabolic syndrome	*Eubacterium*, *Ruminococcus*, *Akkermansia*	Oral gavage FMT in rodents	[126]
5.	Autism spectrum disorder	*Bifidobacterium*, *Prevotella*	Oral FMT	[98]
6.	Multiple sclerosis	*Bifidobacterium*, *Bacteroides fragilis*	FMT in mouse models	[96]
7.	Major depressive disorder	*Butyrivibrio*, *Faecalibacterium*	Oral capsule FMT	[89]
8.	Parkinson's disease	Not specified	Various FMT delivery methods in patients	[95]
9.	Alzheimer's disease	*Alloprevotella*, *Desulfovibrio*	Intragastric FMT in mouse models	[97]
10.	Crohn's disease	*Roseburia*, *Eubacterium*, *Streptococcus*	Endoscopic and colonoscopic FMT	Colman *et al*., 2014
11.	Ulcerative colitis	*Prevotella*, *Parabacteroides*, *Clostridium*, *Fusobacterium*	FMT through colonoscopy and rectal enema	[124]
12.	Irritable bowel syndrome	*Akkermansia*, *Delftia*	Colonoscopy based FMT	[121]
13.	Acute myeloid leukemia	*Ruminococcaceae*, *Lachnospiraceae*	FMT treatment in patients	[127]
14.	Hepatic encephalopathy	*Bifidobacteriaceae*, *Lactobacillaceae*	Oral capsule FMT	[128]
15.	Graft-versus-host disease	*Firmicutes*, *Bacteroidetes*	FMT through nasojejunal tube along with IV steroids	[94]
16.	Advanced melanoma	*Bifidobacteriaceae*, *Lachnospiraceae*	Colonoscopy based FMT	[129]

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it is not limited to well-known microbial taxa. As more metagenomic datasets become available, an integrative metagenomic analysis may help us find general patterns of microbial engraftment and related clinical outcomes.

Fecal microbiota transplantation has become an effective treatment, especially for rCDI. On the other hand, to guarantee safety and effectiveness in its broader application, particularly in elderly individuals with multiple medical conditions, it needs to be carefully standardized. Biological sample banks are essential in order to have a screened, controlled supply of stool and quicken the eligibility of donors. Using pooled donor samples, those banks whether centralized or institution-based, similar to those in the United States also reduce costs while enhancing microbial diversity.[112,113] Several enterotype shifts are promoted when male and female donor donations are combined, and strain-level monitoring using bacterial rrn operon variants has been associated to enhanced metabolic health.[114] The efficiency will be enhanced by the fact that only one donation can produce up to eight doses of FMT.[115,116] Unrelated voluntary donors are preferred over family and friend donors in the past due to ethical issues and absence of diversity. The related donors have the potential to offer gene compatibility but the voluntary donors offer higher microbiota diversity and reduced risk of infection. Considering the microbiota differences between the different life phases, age matched donors are desirable. The schematic profile of the healthy donor selection procedure with the microbiota consortium of FMT preparation and administration pathways in recipient as depicted in Figure 4. Even with the availability of stool banks, finding qualified donors is still challenging. Only about 25% of participants in one study and 10% in another are eligible due to stringent pre-screening and testing procedures. There must be behavioral screenings and tests to eliminate malignant, neurological, autoimmune or psychiatric disorders associated with dysbiosis.[117] Like in blood donor screening, extensive questionnaires and lab work is recommended by the guidelines in the U.S. In genetically linked conditions like IBD, unrelated donors are preferred, but related donors such as intimate partners and maternal relatives may elevate compatibility and immune tolerance. Previous reviews suggested that FMT in related donors in rCDI had more success (93% vs. 84%), but additional examinations did not reveal any significant distinction.[118,119] To enhance microbial viability and stool retention FMT preparation typically involves bowel cleansing, as well as loperamide or proton pump inhibitors. The usual dosages are 250–300 mL of diluent (saline) and 50–60 g of stool. Colonoscopy as the most popular delivery method offers the full access of the colon, but is dangerous to patients with severe colitis. But less invasive, the nasogastric or nasoduodenal tube accesses in the upper GI can cause discomfort or overabundance of bacteria in the small intestine. For a wide range of clinical conditions, more research is required to optimize delivery.[120,121]

Even in patients with multiple medical conditions, FMT is usually considered as safe and well tolerated. Symptoms such as mild fever, diarrhea, bloating, and abdominal pain are common and still remains in 2 days.[122,123] Serious but uncommon side effects include IBD flare-ups, pneumonia, peritonitis, and the spread of pathogens like norovirus, especially in unsupervised "do-it-yourself" cases that have led to cytomegalovirus infection and worsened ulcerative colitis symptoms because donor screening was not sufficient.[124]

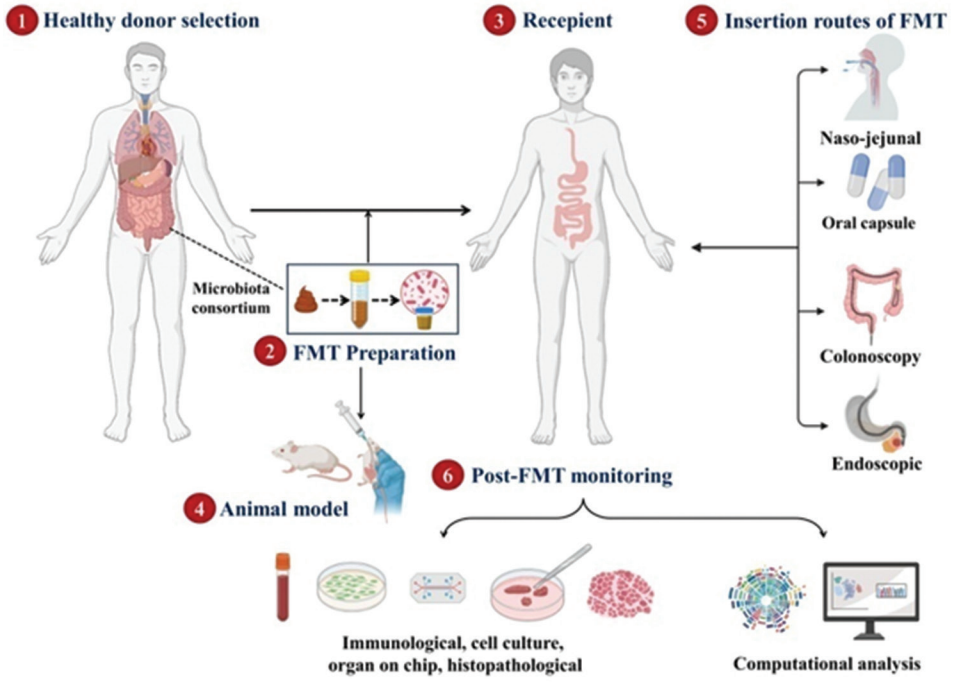

Figure 4: Schematic illustration of the fecal microbiota transplantation (FMT) workflow: donor selection, microbiota preparation, recipient administration through various delivery routes, animal model testing, and post-FMT monitoring

Long-term hazards include the spread of latent infections like hepatitis C and HIV, as well as the emergence of chronic illnesses like colon cancer, obesity, diabetes, IBD, autism, and asthma that are connected to changes in gut microbiota.[119] Stool banks are being regulated, and synthetic microbial consortia are being engineered as standardized substitutes to improve safety and reproducibility.[123]

CHALLENGES AND LIMITATIONS

PMM aims to personalize treatments based on an individual's gutmicrobiota. There are however a number of issues that restrict its application in clinical practice. These are inaccurate data, ethical issues, lack of cause-effect relationships, and at-population disparities in microbiome phenotypes.

Data heterogeneity and lack of standardization

The inconsistency of microbiome data is considered to be one of them. Various sequencing technologies, sample treatment and examination procedures will yield different outcomes. This complicates the opportunity to compare studies and determine some reliable biomarkers.[130] Nearing *et al*. discovered that the use of various statistical tools on identical data can give highly diverse results.[131] Modeling ML is not always able to generalize due to the vast variety of data forms and preprocesses.[132] McMurdie and Holmes cautioned that a common practice of rarefaction usually also results in a wrong conclusion.[133] Instead, they suggest models such as the Negative Binomial. Technical errors during sample storage, DNA extraction and sequencing can also create artifacts. Yang *et al*. and Kumar *et al*. pointed out that 16S rRNA and shotgun sequencing have different strengths and limitations.[127,134] Xia added that no single normalization method works best in all cases. So, International guidelines are needed for collecting, processing and analyzing microbiome data.[135]

Ethical and regulatory issues

The therapies of microbiome, such as FMT, probiotics, and engineered microbes, are ethically questionable. These are consent, data ownership, risk communication and identity. The profiles of microbiome may be accurate privacy indicators, such as vulnerability to disease or eating patterns. Thus, they need to be safeguarded similar to the genetic data.[136] The science is far ahead of the legal and ethical systems. The existing regulations lack clarity as to who holds ownership of microbiome information. When a treatment has been produced based on the microbiota of a person, then there will hardly be any credits or compensations.

Ethics traditionalism grounded in personal consent might not be adequate. Microbiome therapy does not only impact on individual health but on community health also. According to Rhodes, there is a need to make the transition toward the public health ethics, which revolves around collective responsibility.[136] The laws also vary between nations. As an illustration, the U.S. FDA encourages FMT in particular infections but does not provide much information on other treatments.[132] These inabilities to be clear retards innovation and cooperation. Lange *et al*. proposed four guiding principles for microbiome research such as Do Good, Don't Harm, Respect, and Act Justly.[137] They also suggest treating the microbiome as a global common good, with fair and transparent data use.

Causality versus correlation

Several researches associate gut microbes with such diseases as obesity, diabetes, and IBD.[138] However, a majority of them are not a demonstration of cause but a correlation with it.[139] It is the environment and genetics that influence the microbiome such that the changes could be the result of the disease itself rather than its cause. Indicatively, individuals that have MetS tend to present lesser microbial variety and greater Firmicutes-to-Bacteroidetes proportions. Nevertheless, it is not clear whether these trends are a causal factor or a consequence.[127,139] In addition, similar functions are performed by many microbes, and hence taxonomic modification may not have an impact on functionality. Scientists have come up with methods such as Bayesian statistics network models to discover a causality.[140] However, these approaches have issues such as overfitting and non-homogeneous data.[141] It can be assisted with the multi-omics techniques like metabolomics and proteomics. They demonstrate microbial alterations and their impact on biology. However, they are also expensive and complicated methods.[127,134]

Variability across populations

Microbial consortium is influenced by such factors as diet, age, location as well as antibiotics.[127,134] Owing to this, no single definition can be given to a healthy microbiome. According to Kaul *et al*., the same probiotic treatment produced varied results based on the age, BMI and microbiome of the person.[139] This shows the need for personalized treatment. Fonseca *et al*. reported that ML models trained on one group often fail in others.[132] This is due to population-specific microbes and poor data quality. Karwowska *et al*. also found that the most important microbes identified by models differ between datasets. Animal studies show similar issues.[142] Basson *et al*. found that changes in the lab environment cause changes in mouse microbiomes which become less human-relevant.[143] The major part of the microbiome information is based on the Western countries. Projects like the Human Microbiome Project and MetaHIT have left many regions underrepresented. Lange *et al*. emphasized

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that it is necessary to consider low-income and wide-regions people.[137] As a solution, research will have to employ more heterogeneous populations, standardized techniques, and monitor environmental data.

FUTURE DIRECTIONS IN PMM

Advanced technological integration

The way forward is that in the future, AI and ML can be used in conducting a microbiome analysis to make predictions more accurate and then come up with superior personalized treatment plans. It is also a good idea to use the developing fields of AI and ML to investigate gut microbiota to create a diagnostic system and identify new treatments.[7,19] We examine the development and application of some of the more advanced dynamic methods, including unified analytical frameworks and deep learning tools in AI, in detail. To make a breakthrough in the field of personalized and PM in the future, it is highly important to establish dynamic microbiome interstudy and enhance reliable analytical protocols.[144]

Mechanistic understanding and therapeutic targets

More integrative studies will indicate new therapeutic roles to action (such as enzymes or receptors that regulate the interaction of microbiota-secreted molecules with one another and the promotion or modulation of diseases).[145] But to keep the promise of lifelong heart health, more mechanism studies need to move from finding correlations to finding causes and figure out new ways that certain microbes can cause CVDs.[7] The new strategies used to treat the condition have witnessed the development of new approaches involving FMT, engineered probiotics, and microbiome-derived metabolites as potential therapeutic approaches to control immune dysfunction and improve treatment outcomes. In addition, microbiome profiling paired with AI, and microbial engineering using CRISPR can potentially be used in personalized medicine, where microbial ecosystems are controlled and modulated specifically based on individual patient diagnosis and treatment.

Personalized nutrition and PM

Individuals with a specific gut microbial profile might have better clinical outcomes and adjusted care to benefit the distinct patient population.[17] Applying ML to high-quality dietary intake data will improve our ability to predict microbiome responses and translate those predictions into personalized recommendations.[146] Practical strategies may include integrating gut microbiota and blood metabolite markers to stratify patients, then offering individualized diet plans, lifestyle changes, and evidence-based probiotic or prebiotic treatments at appropriate life stages.[7]

Clinical translation and implementation

Although with promising outcomes, the following challenges still persist: standardized protocols will be required, an adequately robust clinical trial, and an affordable pathway of implementation.[147] Another complication of clinical translation is interindividual variability in microbiomes, gaps in our knowledge regarding the mechanisms, and regulatory obstacles.[13] Addressing these limitations is essential to realize the full potential of microbiome-based therapies for immune modulation, autoimmunity, and cancer.

IBD-RESPONSE is a program that focuses on realizing the combination of multi-omics data to create predictive algorithms to respond to treatment.[148] In the future, biomarker-based and targeted treatment stratification and strategic control of gut microbes could be offered to patients. Combined with AI-driven analytics, microbiota-targeted interventions promise improved diagnostics and clinical outcomes, but harmonized methods and additional high-quality primary studies are required to consolidate the evidence base.[16]

Innovative monitoring and intervention technologies

Dysbiosis of the gut microbiota is a major cause of many disorders. This implies that microbiota-based therapies and other technologies, such as biosensors that monitor the real-time health of the gut, non-invasive diagnostic tools, and automated bio foundries, could all come into play to do so through non-invasive analyses of feces and saliva in a non-centralized, frequent manner. This would aid in on-time human microbiota monitoring and respond to the specific diet intervention in the restoration and promotion of individual gut redox equilibrium.[149]

Longitudinal studies are necessary to establish how certain diets and food ingredients define the gut microbiome in the long run and define interindividual variation.[146] Although this has improved methodology, there is still a need to verify the analytical workflows and integrate data resources of longitudinal multi-omics studies due to the lack of agreed gold standards.[144] We also tackle the issues of genetic stability, environmental safety, and the necessity of strong regulatory knowledge, and the fact that more research is still needed to make microbiome interventions safe and effective.

Integrative and holistic approaches

The multi-omics and improved microbial therapeutics could propel the gut microbiome to be the support system of therapeutic use to become a mainstay of PM soon.[13] A multidisciplinary approach may aid in improving the future of patients with PM as it may discover the ways of how the microbiome and human health influence each other in

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a complex manner.[12] This review will examine the role of Ayurveda in bringing Ayurvedic ancient knowledge and modern scientific discoveries together to ascertain its possible role in offering metabolic, immune, and inflammatory health using Ayurveda.[150] This integrative method provides a good prospective practice to adopt microbiome-specific therapeutic development to meet preventive and therapeutically focused approaches that are in line with the current trend of individualized and holistic treatment. All of these directions lead to a transformative period in precise microbiome medicine, where personalized gut microbiota-based therapy will become a part of healthcare delivery, and it will provide unparalleled opportunities in enhancing patient outcomes in a variety of populations and diseases.

CONCLUSION

In the case of medical research, PMM is pushing the boundaries. Coming hotfooting off the heels of the initial discoveries, PMM is basically changing the way we can stop, diagnose, and treat various health conditions in individuals, and does so by getting to know each person's one-of-a-kind microbial fingerprint, how their microbes interact with their body, and the environment they live in. Well-known as different from the traditional approach that uses the same treatment for everyone, PMM lets you make precise adjustments to a person's microbiome using microbe-based markers, medications, and customized diets. This review took a look at the components of PMM and how breakthroughs in super-fast sequencing, metagenomics, metabolic analysis, and computer simulations have enabled us to get an extremely detailed understanding of the microbiome. The advent of fusion of multi-omics data, AI-driven insights, and real-time sensors has turned a static description of the microbiome into a dynamic and actionable understanding of how it functions, and what we can do to change it. With an ever-growing body of clinical proof that PMM is effective in a wide range of fields, from GI problems like Crohn's disease and IBS to MetS and cancer, the case for its future clinical use is strong, but still, there are obstacles in the way. As for the intricate dance between the microbiome and disease, we are still on the cusp of understanding what causes these relationships. We need to standardize the way we collect and analyze microbiome samples, and test microbiome-based treatments in large, randomized clinical trials; otherwise, they may not hold any real value. The regulatory frameworks for live biotherapeutics, engineered microbes, and microbiome-derived diagnostics are also in flux. If the leap from the lab to the patient's bed is to be achieved, a great deal of ethical issues has to be addressed in advance, including patient privacy, data ownership, and fair access to these microbiome-based treatments. In short, the path from bench to bedside won't be cleared up until we have very clear regulations and an ironclad infrastructure PMM faces obstacles, but its outlook is strong. Diagnostic tools, transplantation methods, AI-driven microbiome analysis, and tailored nutrition solutions are evolving quickly. When combined with digital health platforms, wearable sensors, and systems that capture patient data over time, PMM will support near-real-time monitoring and dynamic treatment adjustments in routine clinical practice. Furthermore, when PMM works with other precision fields like genomics, epigenetics, and pharmacometabolomics, it will help us understand human health in a more complete way, at the level of the whole system. PMM treats the microbiome as a fundamental determinant of health, not merely an addon to existing PM approaches. As healthcare becomes more personalized and predictive, PMM will be essential. To implement microbiomebased precision care at scale, we need teamwork across specialties, robust new tools, meaningful patient involvement, and policy changes that enable clinical adoption.

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